UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,777	07/13/2001	James Chen	600057.446C1	5768

20985 7590 11/17/2008
FISH & RICHARDSON, PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
11/17/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	09/905,777	CHEN, JAMES	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18, 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 and 25-28 are pending and under consideration. It is noted that the amendment filed August 7, 2008 erroneously lists claims 13, 14 and 26 as "withdrawn".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-18, 27 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is vague and indefinite in the recitation of "target cell that comprises the lesion in the arterial vascular system". It is unclear how the target cell can "comprise" the lesion itself since said lesion is multicellular. Amendment to “target cells of the lesion” would overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods relying on antibodies which selectively bind to epitopes which are part of a vascularized tumor, does not reasonably provide enablement for methods relying on antibodies which selectively bind to receptors which are part of lesions of the vascular system, or methods relying on the direct binding of heparin, angiotensin II, LDL or VLDL to receptors of the vascular lesion or methods relying The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

It is well known in the art that antibodies can be used to specifically target diagnostic or therapeutic agents in vivo to specific sites via antigen-antibody interactions which are specific to the targeted tissues. However, the instant claims 13 and 26 encompass ligands which are LDL, VLDL, heparin or angiotensin II which would not be specific for the targeting of the instant photosensitizing agents to a vascular lesion. There are no teachings in the specification or art of record which would support the use of a targeting agent to a vascular lesion which was based on the specific binding of biotin/streptavidin, a chemokine, a growth factor, LDL, VLDL, heparin or angiotensin II to vascular lesions. Chen et al (Journal of the American Chemical Society, 2007, Vol, 129, pp. 5798-5799) teach that LDL would not be useful as a targeting agent because normal tissues such as the liver, adrenal and reproductive organs all express high levels of the cognate receptor, and thus would compete for an administered drug conjugated to LDL (page 5798, first column, lines 11-15). Thus, the targeting of arterial plaque as suggested by the instant specification would also have the same drawback of competing with the liver, adrenals and reproductive organs all of which highly express the LDL receptor. Further, Chen et al teach that circulating apoproteins in vivo have affinity for LDL and would bind to the surface of an administered LDL conjugate providing an increased affinity for scavenger receptors and the LDL receptors (page 5799, second column, lines 17-20). The specification fails to address or provide guidance to overcome the above problems regarding lack of selectivity relative to normal organs and tissues. Chen et al further teach that the exposed active lysine portions of LDL play a central role in recognition and binding to LDL receptor (page 5798, first column, second paragraph, lines 1-5). It is common in the art to make a conjugate using lysine residues of a protein (Gozzini et al, U.S. 6,719,958, column 2, lines 7-10). In the instant case using the exposed lysine residues of the apoB protein associated with the LDL would result in loss of targeting to the LDL receptor. The specification fails to teach how to make a conjugate with LDL or VLDL that would preserve binding to the cognate receptor. One of skill in the art would be further

subjected to undue experimentation in order to make a conjugate with LDL or VLDL that would preserve binding to the targeted receptor.

The specification states that heparin has a high binding capacity to FGF, and Angiotensin II binds to receptors on vascular smooth muscle cells (page 18, lines 13-15). The specification concludes that both heparin and angiotensin II can be used to localize a photosensitizer to a vascular region to be treated. The specification provides no indication as to the nature of the lesion that would differentially bind heparin or angiotensin II relative to other normal organs or tissues. The post-filing art indicates that heparin must be conjugated to an antibody that binds to cross-linked fibrin in order to be selectively delivered to sites of restinosis (Thomas et al, Journal of Controlled Release, 2004, Vol. 100, pp. 357-377). It can be concluded from this reference that heparin lacks specific targeting ability. Thus, one of skill in the art would be subject to undue experimentation in order to use a conjugate of a photosensitizer with heparin or angiotensin II because there is no evidence of selective binding to a targeted lesion over that of normal organs and tissues.

Claim 2 is drawn to a method comprising administering to a subject a first conjugate comprising a first member of a ligand-receptor binding pair conjugated to an antibody or an antibody fragment, wherein the antibody or antibody fragment selectively binds to the target cell of a vascular lesion. Claim 1 is drawn to a method comprising administration to a subject a ligand conjugate, wherein said ligand selectively binds to a receptor on target cells of a lesion in the vascular system. Thus both claims require a specific binding agent for vascular lesion wherein said agent can be therapeutically effective when administered in vivo. The specification suggests that antibodies which bind to thick or thin neointimas, arterial plaques, vascular smooth muscle cells and/or the abnormal extracellular matrix can be used (page 6, lines 30-31). The specification does not describe any of the antibodies or the specific antigen or epitopes that are being targeted. The prior art at the time of filing (Tsimikas et al (WO98/21581) indicates that reagents which have been investigated for binding to atherosclerotic plaque components include radiolabeled LDL, apolipoprotein B, autologous platelets, antifibrin antibodies and components of smooth muscle proliferation, but that these reagents lack specificity to discern the lesion from the components of normal vessel walls and blood (page 1, lines 11-21). Tsimikas et al describe two antibodies (MDA2 and NA59, page 2, line 9 to page 3, line 9) which function to specifically

bind to atherosclertoic plaque versus normal vessel walls and blood. Ditlow et al (U.S. 5,811,248) teach that antibodies to oxidized or otherwise modified lipoproteins are not specific to plaque as said antigens have been found in normal artery and or other normal tissues, and that some antibodies, although promising in the Watanabe rabbit model fail to provide specificity when used to target human plaque in vivo (column 3, lines 23-35). Ditlow et al teach the monoclonal antibody of Z2D3 for targeting in vivo plaque (column 3, line 65 to column 4, line 2 and column 4, lines 19-21). Matsueda et al, (WO 87/06263, see claims) teaches an antibody to cross-linked fibrin. However, taken as a whole, the description of only a few antibodies in the prior art which have the ability to distinguish plagues or blood clots from the normal vessel walls and blood does not provide enablement for the broad requirement of an antibody which specifically binds to target cells that are part of a vascular lesion.

Claim 1 encompasses ligands which, when given the broadest reasonable interpretation, are not limited to antibodies. Without a description as to the receptors to which the ligands must bind, one of skill in the art would be subject to undue experimentation because it would be first necessary to determine ligands which specifically bind to targeted lesions of the vascular system before the claimed method of treatment can be carried out.

Claims 1-18 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims require ligands or antibodies which specifically bind to target cells within vascular lesions that include arterial plaques. The specification suggests that the ligand can be an antibody which specifically binds to neointimas, arterial plaques, vascular smooth muscle cells and/or the abnormal extracellular matrix of the site to be treated (page 6, lines 30-31). The specification lacks a description of such antibodies or a description of the complete protein or carbohydrate structure to which said antibodies specifically bind. The art at the time of filing describes only a few antibodies (Tsimikas et al (WO98/21581), Matsueda et al, (WO 87/06263) and Ditlow et al, U.S. 5,811,248) above. However, the description of three antibodies is not a satisfactory description of a genus of antibodies which can specifically bind to

a vascular lesion, because said lesion is complex, including multiple cell types and products produced therefrom. Based on the low level of disclosure in the art at the time of filing and the lack of description by the instant specification for antibodies that specifically bind to cells in vascular lesion, one of skill in the art would reasonable conclude that applicant was not in possession of the instant methods which rely on said specific antibodies and ligands.

Applicant argues that the specification is enabling for the use of photosensitizer targeted conjugated of LDL, VLDL, heparin and angiotensin II. This has been considered but not found persuasive for the reasons set forth above. Applicant argues that claim 2 recites a first member of a ligand-receptor binding pair conjugated to an antibody. Applicant argues that given the state of the art, antibody targeting is well known. This has been considered but not found persuasive. Clearly claim 2 encompasses a pretargeting method. However, without a full description of the antibodies or the antigens to be targeted, one of skill in the art would not be subject to undue experimentation in order to make antibodies which would be conjugated to the broadly claimed " lesion in the vascular system".

All other rejections and objections as set forth in the prior office action are withdrawn in light of applicants amendments and arguments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643